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Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults (Review)

Derry S, Derry CJ, Moore RA

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[Intervention Review]

Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

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ABSTRACT

Background

Combining two different analgesics in fixed doses in a single tablet can provide better pain relief than either drug alone in acute pain. This appears to be broadly true across a range of different drug combinations, in postoperative pain and migraine headache. Fixed-dose combinations of ibuprofen and oxycodone are available, and the drugs may be separately used in combination in some acute pain situations.

Objectives

To assess the analgesic efficacy and adverse effects of a single oral dose of ibuprofen plus oxycodone for moderate to severe postoperative pain.

Search methods

We searched the Cochrane Central Register of Controlled Trials, (CENTRAL), on *The Cochrane Library*, (Issue 4 of 12, 2013), MEDLINE (1950 to 21st May 2013), EMBASE (1974 to 21st May 2013), the Oxford Pain Database, ClinicalTrials.gov, and reference lists of articles.

Selection criteria

Randomised, double-blind clinical trials of single dose, oral ibuprofen plus oxycodone compared with placebo or the same dose of ibuprofen alone for acute postoperative pain in adults.

Data collection and analysis

Two review authors independently considered trials for inclusion in the review, assessed quality, and extracted data. We used the area under the pain relief versus time curve to derive the proportion of participants prescribed ibuprofen plus oxycodone, ibuprofen alone, oxycodone alone, or placebo with at least 50% pain relief over six hours, using validated equations. We calculated relative risk (RR) and number needed to treat to benefit (NNT). We used information on use of rescue medication to calculate the proportion of participants requiring rescue medication and the weighted mean of the median time to use. We also collected information on adverse events.

Main results

Searches identified three studies involving 1202 participants. All examined the same dose combination. Included studies provided data from 603 participants for the comparison of ibuprofen 400 mg + oxycodone 5 mg with placebo, 717 participants for the comparison of ibuprofen 400 mg + oxycodone 5 mg with ibuprofen 400 mg alone, and 471 participants for the comparison of ibuprofen 400 mg + oxycodone 5 mg with oxycodone 5 mg alone.

The proportion of participants achieving at least 50% pain relief over 6 hours was 60% with ibuprofen 400 mg + oxycodone 5 mg and 17% with placebo, giving an NNT of 2.3 (2.0 to 2.8). For ibuprofen 400 mg alone the proportion was 50%, producing no significant difference between ibuprofen 400 mg + oxycodone 5 mg and ibuprofen 400 mg alone. For oxycodone 5 mg alone the proportion was 23%, giving an NNT for ibuprofen 400 mg + oxycodone 5 mg compared with oxycodone alone of 2.9 (2.3 to 4.0).

Ibuprofen + oxycodone resulted in longer times to remedication than with placebo. The median time to use of rescue medication was more than 5 hours for ibuprofen 400 mg + oxycodone 5 mg, and 2.3 hours or less with placebo. Fewer participants needed rescue medication with ibuprofen + oxycodone combination than with placebo or ibuprofen alone. The proportion was 40% with ibuprofen 400 mg + oxycodone 5 mg, 83% with placebo, 53% with ibuprofen alone, and 83% with oxycodone alone, giving NNT to prevent one patient needing rescue medication of 2.4 (2.0 to 2.9), 11 (6.1 to 56), and 2.6 (2.1 to 3.4) for comparisons of ibuprofen 400 mg + oxycodone 5 mg with placebo, ibuprofen alone, and oxycodone alone, respectively.

The proportion of participants experiencing one or more adverse events was 25% with ibuprofen 400 mg + oxycodone 5 mg, 25% with placebo, 26% with ibuprofen alone, and 35% with oxycodone alone; they were not significantly different. Serious adverse events were reported only after abdominal surgery 6/169 with the combination, 1/175 with ibuprofen alone, 3/52 with oxycodone alone, and 1/60 with placebo. Withdrawals for reasons other than lack of efficacy were fewer than 5% and balanced across treatment arms.

Authors' conclusions

The combination of ibuprofen 400mg + oxycodone 5mg provided analgesia for longer than oxycodone alone, but not ibuprofen alone (at the same dose). There was also a smaller chance of needing additional analgesia over about eight hours, and with no greater chance of experiencing an adverse event.

PLAIN LANGUAGE SUMMARY

Single dose oral ibuprofen plus oxycodone for acute postoperative pain

Acute pain is often felt soon after injury, and most people who have surgery will have pain of moderate or severe intensity without treatment for their pain. In most, though not all, circumstances, the pain can be treated with oral analgesics. Many oral analgesics are available, and this review is one of a series examining how effective each one is, at particular doses.

This review examines a combination of fixed doses of ibuprofen and oxycodone. Both are commonly used analgesics, which work by different mechanisms. We know that combining different analgesics in the same tablet gives good pain relief to more people than either analgesic alone, at the same dose.

This review found data in three clinical trials, involving 1202 people with moderate or severe pain after having wisdom teeth removed or after abdominal or pelvic surgery. These situations are used commonly to test analgesic effectiveness, because results are applicable to other forms of acute pain after trauma. Different types of surgery give very similar estimates of the effectiveness of analgesic drugs.

Ibuprofen 400 mg plus oxycodone 5 mg provided effective pain relief for about 6 in 10 (60%) of participants, compared with just under 2 in 10 (17%) of participants with placebo. The analgesic effects lasted longer and there were no more adverse events with the combination than with placebo. The combination provided effective pain relief to about the same proportion of people as did ibuprofen alone, but there was a lower chance of needing additional analgesia with the combination.

BACKGROUND

Description of the condition

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury and/or nerve injury. The management of postoperative pain and inflammation is a critical component of patient care.

This is one of a series of reviews whose aim is to increase awareness of the range of analgesics that are potentially available, and present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in an overview (Moore 2011a), and related individual reviews include ibuprofen (Derry 2009), paracetamol (Toms 2008), paracetamol plus codeine (Toms 2009), codeine (Derry 2010), and oxycodone with or without paracetamol (Gaskell 2009).

Description of the intervention

Acute pain trials

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are small, allowing no reliable conclusions to be drawn about safety. To show that the analgesic is working, it is necessary to use placebo (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called *rescue analgesia*, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is hence important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double-blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following four to six hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful.

Ibuprofen

Ibuprofen was developed in the 1960s and is used extensively throughout the world for relief of pain and inflammation in both acute and chronic conditions. It is available over the counter in most countries, usually as 200 mg tablets, with 1200 mg as the recommended maximum daily dose for adults. Under medical supervision, up to 3200 mg daily may be taken, divided into three doses. Soluble salts of ibuprofen have lower (better) NNTs (Derry 2009).

A major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site because it inhibits platelet aggregation (Forrest 2002), and from the upper gastrointestinal tract, especially in patients stressed by surgery, the elderly, frail, or dehydrated. Other potentially serious adverse events include acute liver injury, acute renal injury, heart failure, and adverse reproductive outcomes (Hernandez-Diaz 2001). Complications are more likely to occur with chronic use, and NSAIDs present fewer risks if used in the short term, as in the treatment of postoperative pain (Rapoport 1999).

Oxycodone

Oxycodone is a semi-synthetic, strong opioid agonist, developed in the early 20th century, and chemically related to codeine. It is considered to be comparable to morphine for efficacy, and similar for adverse events, with the exception of hallucinations, which tend to occur rarely with oxycodone (Poyhia 1993). Its analgesic potency makes it useful for the management of severe pain, usually acute postoperative, post-traumatic or cancer pain. For oral

administration oxycodone is available in 5 mg, 10 mg, and 20 mg capsules, which are given 4 to 6-hourly to a daily maximum of 400 mg. A modified (slow) release formulation is available as tablets up to 80 mg. Repeated administration of oxycodone can cause dependence and tolerance, and its potential for abuse is well known. Regulation of supply varies between countries, but in many, all oxycodone preparations are controlled substances. Oxycodone is commonly combined with milder analgesics, such as paracetamol, and more recently ibuprofen. The purpose is to increase efficacy by simultaneously using drugs with distinct mechanisms of action with the aim of reducing the amount of opioid required for a given level of response, and so reducing adverse events (Edwards 2002).

How the intervention might work

NSAIDs reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. Ibuprofen, like most NSAIDs, causes reversible inhibition of the cyclooxygenases, which interferes with thromboxane and prostaglandin synthesis, and increases production of anti-inflammatory lipoxins.

The mechanism of action of oxycodone is not well understood. It has affinity for the μ-, -, and δ-opioid receptors, and probably exerts its analgesic effect via μ- and -receptors. Binding initiates a series of intracellular events leading to hyperpolarisation of the nerve cell which, together with reduced release of neurotransmitters, results in reduced transmission of nerve stimulation (Ordóñez Gallego 2007). Oxycodone appears to be actively transported across the blood-brain barrier, so that concentrations in the brain are higher than in the plasma. This differs from morphine, where the concentrations in the plasma are higher than in the brain, and may explain the difference in efficacy observed for similar plasma concentrations (Kalso 2007).

Combination analgesics

We now have convincing evidence that combining two analgesics can provide additional levels of analgesia in acute pain and headache (Moore 2011b; Moore 2012), and that the drug-specific effects are essentially additive. Results confirm that the assumption that the efficacy of combination analgesics is the sum of the efficacies of the individual analgesic components is broadly true across a range of different drug combinations, in postoperative pain and migraine headache, and when tested in the same and different trials (Moore 2012). There is no convincing evidence for combination analgesics in chronic pain, however (Chaparro 2012).

A fixed dose combination tablet, containing 400 mg ibuprofen and 5 mg oxycodone (Combunox™), is now available for short-term relief of moderate to severe pain.

Why it is important to do this review

Both ibuprofen and oxycodone are widely available and have proven efficacy for relief of acute postoperative pain (Derry 2009; Gaskell 2009). Use of oxycodone is commonly limited by opioid-related adverse events, and combining it with paracetamol significantly enhances its efficacy (Gaskell 2009). It is important to know how the new combination of ibuprofen and oxycodone compares with other analgesics assessed in the same way (Moore 2011a).

OBJECTIVES

To assess the analgesic efficacy and adverse effects of a single oral dose of ibuprofen plus oxycodone for moderate to severe postoperative pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies of double-blind trials of single dose oral ibuprofen plus oxycodone compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. We included multiple dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first arm were presented separately.

We excluded the following.

- Review articles, case reports, and clinical observations.
- Studies of experimental pain.
- Studies where pain relief is assessed only by clinicians, nurses, or caregivers (i.e. not patient-reported).
- Studies of less than four hours duration or studies that fail to present data over four to six hours postdose.

For postpartum pain, we would include studies if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; we would exclude studies investigating pain due to uterine cramps alone.

Types of participants

We included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery. For studies using a visual analogue scale (VAS), we considered that pain intensity of greater than 30 mm equates to pain of at least moderate intensity (Collins 1997).

Types of interventions

Ibuprofen plus oxycodone or matched placebo administered as a single oral dose for postoperative pain. The ibuprofen and oxycodone could be administered as separate tablets taken together, or in a combined tablet. We included all dose combinations.

Types of outcome measures

We collected the following data where available.

- Participant characteristics.
- Patient reported pain at baseline (physician, nurse, or care giver reported pain were not included in the analysis).
- Patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity or pain relief in the form of VAS or categorical scales, or both).
- Patient global assessment of efficacy (PGE), using a standard categorical scale.
- Time to use of rescue medication.
- Number of participants using rescue medication.
- Number of participants with one or more adverse events.
- Number of withdrawals (all-cause, adverse events).

Primary outcomes

Participants achieving at least 50% pain relief over 4 to 6 hours.

Secondary outcomes

- Median (or mean) time to use of rescue medication.
- Participants using rescue medication.
- Participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event.
- Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication).

Search methods for identification of studies

Electronic searches

We searched the following databases:

- The *Cochrane Central Register of Controlled Trials* (CENTRAL) on *The Cochrane Library*, (Issue 4, 2013).
- MEDLINE (via OVID) (1950 to 21 May 2013).
- EMBASE (via OVID) (1974 to 21 May 2013).
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 1 for the CENTRAL search strategy, Appendix 2 for the MEDLINE search strategy and Appendix 3 for the EMBASE search strategy. We did not limit the searches by language.

Searching other resources

We searched for additional studies in reference lists of retrieved articles and reviews, and in clinicaltrials.gov. We attempted to contact the manufacturer (Forest Laboratories), but received no response.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies that might be included in the review. Disagreements were resolved by consensus or referral to a third review author.

Data extraction and management

Two review authors extracted data and recorded them on a standard data extraction form. One review author entered data suitable for pooling into RevMan 5.1 (RevMan 2011).

Assessment of risk of bias in included studies

Two review authors independently assessed each study using a three-item, five-point scale (Jadad 1996b), and agreed a consensus score.

The scale used is as follows.

- Is the study randomised? If yes- one point.
- Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.
- Is the study double-blind? If yes add one point.
- Is the double-blind method reported and is it appropriate? If yes add one point, if no deduct one point.
- Are the reasons for patient withdrawals and dropouts described? If yes add one point.

We also completed a 'Risk of bias' table, using methods adapted from those described by the Cochrane Pregnancy and Childbirth Group. Two authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and resolved any disagreements by discussion. The following were assessed for each study.

- Random sequence generation (checking for possible selection bias). The method used to generate the allocation sequence was assessed as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) - these studies would be excluded; unclear risk of bias.
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. The methods were assessed as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth) - theses studies would be excluded; unclear risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). The methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received were assessed. Studies were considered at low risk of bias if they stated that they were blinded and described the method used to achieve blinding (e.g. identical tablets; matched in appearance and smell), or at unknown risk if they stated that they were blinded, but did not provide an adequate description of how it was achieved. Single blind and open studies would be excluded.
- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Nüesch 2010). Studies were considered at low risk of bias if they had ≥ 200 participants, at unknown risk of they had 50 to 200 participants, and at high risk if they had < 50 participants.

Measures of treatment effect

We used relative risk (or 'risk ratio', RR) to establish statistical difference. We used numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.
We used the following terms to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occur with treatment than with control (placebo or active) we used the term the *number needed to treat to prevent one event* (NNTp).
- When significantly more adverse outcomes occur with treatment compared with control (placebo or active) we used the term the *number needed to harm or cause one event* (NNH).

Unit of analysis issues

The unit of analysis was the individual patient.

Dealing with missing data

The only likely issue with missing data in these studies is from imputation using last observation carried forward when a patient requests rescue medication. We have previously shown that this does not affect results for up to six hours after taking study medication (Barden 2004).

Assessment of heterogeneity

We examined heterogeneity visually using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies.

Data synthesis

We followed QUOROM guidelines (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used number of participants randomised to each treatment group who took the study medication. We planned to analyse for different doses separately.
For each study we converted the mean TOTPAR, SPID, VAS TOTPAR, or VAS SPID (Appendix 4) values for active and placebo to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991), and calculated the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b). We then converted these proportions into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. We used this information on the number of participants with at least 50%maxTOTPAR for active and placebo to calculate relative benefit or relative risk, and number needed to treat to benefit (NNT).
We accepted the following pain measures for the calculation of TOTPAR or SPID.

- Five-point categorical pain relief (PR) scales with comparable wording to 'none, slight, moderate, good or complete'.
- Four-point categorical pain intensity (PI) scales with comparable wording to 'none, mild, moderate, severe'.
- VAS for pain relief.
- VAS for pain intensity.

If none of these measures was available, we would use the number of participants reporting 'very good or excellent' on a five-point categorical global scale with the wording 'poor, fair, good, very good, excellent' for the number of participants achieving at least 50% pain relief (Collins 2001).
For each treatment group we extracted the number of participants reporting treatment-emergent adverse effects, and calculated relative benefit and risk estimates with 95% confidence intervals (CI)

using a fixed-effect model (Morris 1995). We calculated NNT and number needed to treat to harm (NNH) with 95% CIs using the pooled number of events using the method devised by Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the relative risk or relative benefit did not include the number one.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to determine the effect of dose and presenting condition (pain model: dental versus other postoperative pain). A minimum of two studies and 200 participants had to be available in any subgroup or sensitivity analysis (Moore 1998), which would be restricted to the primary outcome (50% pain relief over four to six hours) and the dose with the greatest amount of data. We would determine significant differences between NNT, NNTp, or NNH for different groups in subgroup and sensitivity analyses using the z test (Tramèr 1997).

Sensitivity analysis

We planned sensitivity analyses for quality score (two versus three or more) and trial size (39 or fewer versus 40 or more per treatment arm).

RESULTS

Description of studies

Included studies

We identified three studies, with 1202 participants, that fulfilled the inclusion criteria (Litkowski 2005; Singla 2005; van Dyke 2004). Details of individual studies are in the Characteristics of included studies table.

All of the included studies recruited participants aged 12 years or older (mean ages ranged from 19 to 42 years), and the majority of participants were female (56% to 100% in individual studies). The review protocol specified that participants should be aged at least 15 years old, and although one study (Litkowski 2005) included participants aged 12 years or more, the lower limit of the standard deviation of the mean age was 15 years, so we decided to include it. One study (Singla 2005, 456 participants) included women who had undergone abdominal or pelvic surgery, and the other two included men and women who had undergone surgical extraction of at least two ipsilateral, bony, impacted third molars. Participants were required to be in good general health, and were excluded if they had any significant comorbidity that contraindicated use of any study medication, or might interfere with the study conduct. They were also excluded if they had taken any short-acting analgesics within six or eight hours of surgery, or long-acting analgesics within 24 or 48 hours, and systemic steroids within 72 hours. In Singla 2005, no opioids via patient controlled analgesia was permitted within 30 minutes. Participants were also required to abstain from alcohol, caffeine, and tobacco for 8h before surgery and until completion of 6h observation period.

In all studies participants took a single dose of their medication when baseline pain reached a moderate or severe intensity. Pain intensity and pain relief were measured at set time intervals after dosing on standard 4- and 5-point scales respectively. All studies also carried out a patient global evaluation of treatment at the end of treatment using a standard 5-point scale.

Studies used placebo and active comparators. The following treatments were administered:

- Ibuprofen 400 mg + oxycodone 5 mg (Litkowski 2005; Singla 2005; van Dyke 2004), n = 418
- Ibuprofen 400 mg (Singla 2005; van Dyke 2004), n = 361
- Oxycodone 5 mg (Singla 2005; van Dyke 2004), n = 115
- Paracetamol 325 mg + oxycodone 5 mg (Litkowski 2005), n = 61
- Paracetamol 500 mg + hydrocodone 7.5 mg (Litkowski 2005), n = 62
- Placebo (Litkowski 2005; Singla 2005; van Dyke 2004), n = 185

Excluded studies

We identified no studies for which the full paper had to be read before exclusion. No PRISMA flowchart was required.

Risk of bias in included studies

All studies were randomised and double blind, and reported on withdrawals; two studies (Singla 2005; van Dyke 2004) scored 4/5 on the Oxford Quality Score, and the other (Litkowski 2005) scored 3/5. Points were lost due to failure to report the method used to generate the randomisation schedule or to maintain blinding. It is likely that this is a failure of reporting rather than a flaw in the methods.

Risk of bias was also assessed using the Risk of bias tool (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

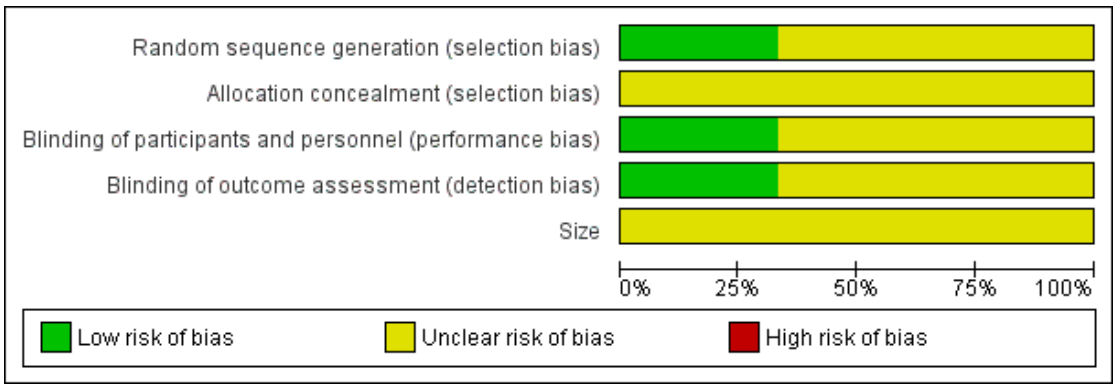
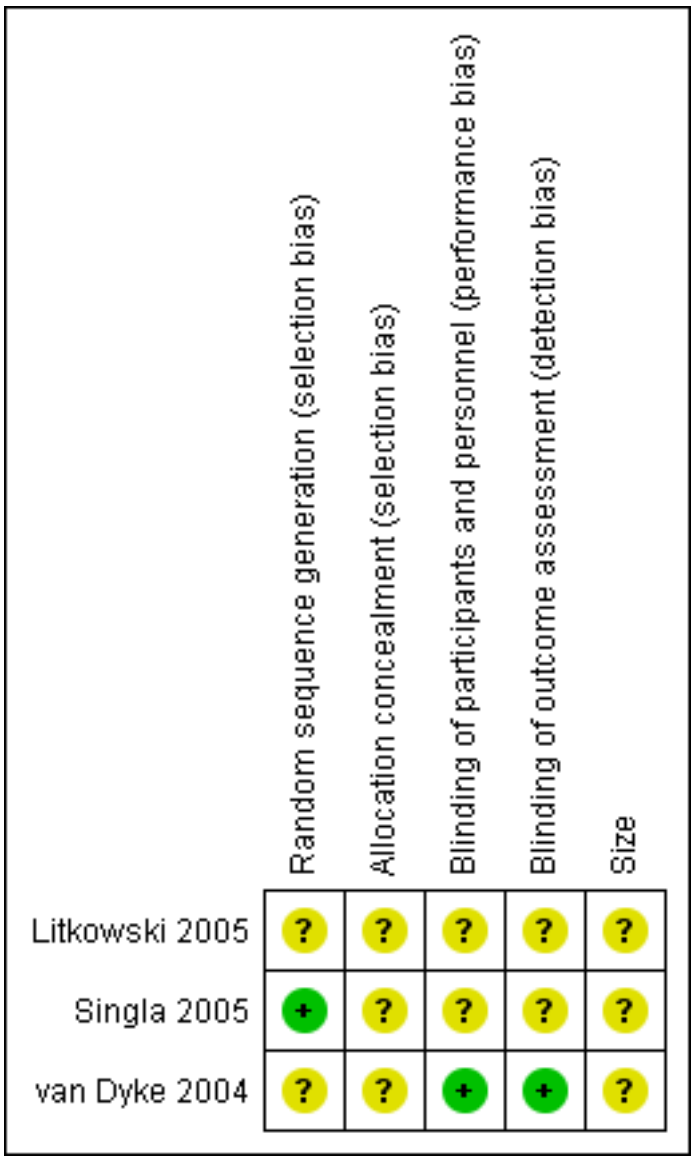


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Details for each study are in the Characteristics of included studies table.

Allocation

All studies reported that they were randomised, but only one (Singla 2005) properly described the method used to generate the schedule. None of the studies described the methods used to conceal the random allocation.

Blinding

All studies were double blind but only one (van Dyke 2004) adequately described how this was achieved.

Other potential sources of bias

Treatment group size was an issue. Small studies are thought to be at increased risk of bias, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised. None of the treatment groups in this review was large enough to be confident that bias would be avoided, and although none had treatment group sizes that put them at high risk of bias, all the placebo and oxycodone groups were very close to our predefined cut-off.

Effects of interventions

Analysis was limited by only one dose of ibuprofen + oxycodone being tested, and only two of the three included studies having treatment arms using the individual components alone. Results for individual studies are provided in Appendix 5 (analgesia and use of rescue medication) and Appendix 6 (adverse events and withdrawals).

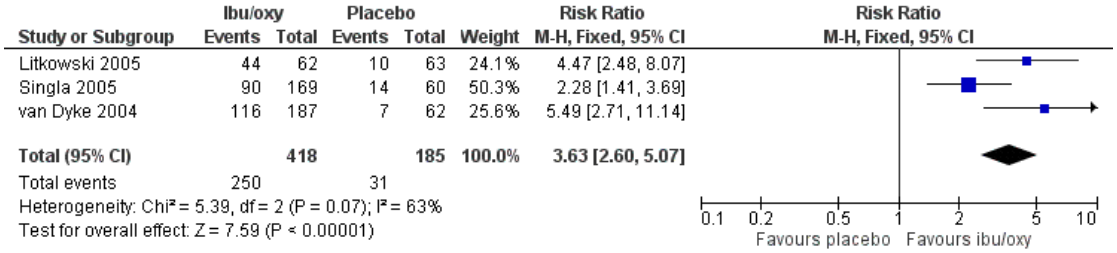
Participants with at least 50% pain relief over 4 to 6 hours

Ibuprofen 400 mg + oxycodone 5 mg versus placebo

All three studies included comparisons of ibuprofen 400 mg + oxycodone 5 mg versus placebo (603 participants).

- The proportion of participants with ≥ 50% pain relief with ibuprofen + oxycodone was 60% (250/418, range 53% to 71%);
- The proportion of participants with ≥ 50% pain relief with placebo was 17% (31/185, range 11% to 23%);
- The relative benefit of treatment compared with placebo was 3.6 (2.6 to 5.1); the NNT was 2.3 (2.0 to 2.8) (Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo, outcome: 1.1 Participants with ≥ 50% pain relief at 6 hours.



Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg alone

Two studies (Singla 2005; van Dyke 2004) included comparisons of ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen alone (717 participants).

- The proportion of participants with ≥ 50% pain relief with ibuprofen + oxycodone was 58% (206/356, range 53% to 62%);
- The proportion of participants with ≥ 50% pain relief with ibuprofen 400 mg was 50% (182/361, range 44% to 56%);
- The relative benefit of the combination compared with ibuprofen alone was 1.2 (1.00 to 1.3); the NNT was not calculated (Analysis 2.1).

Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg alone

Two studies (Singla 2005; van Dyke 2004) included comparisons of ibuprofen 400 mg + oxycodone 5 mg versus oxycodone alone (471 participants).

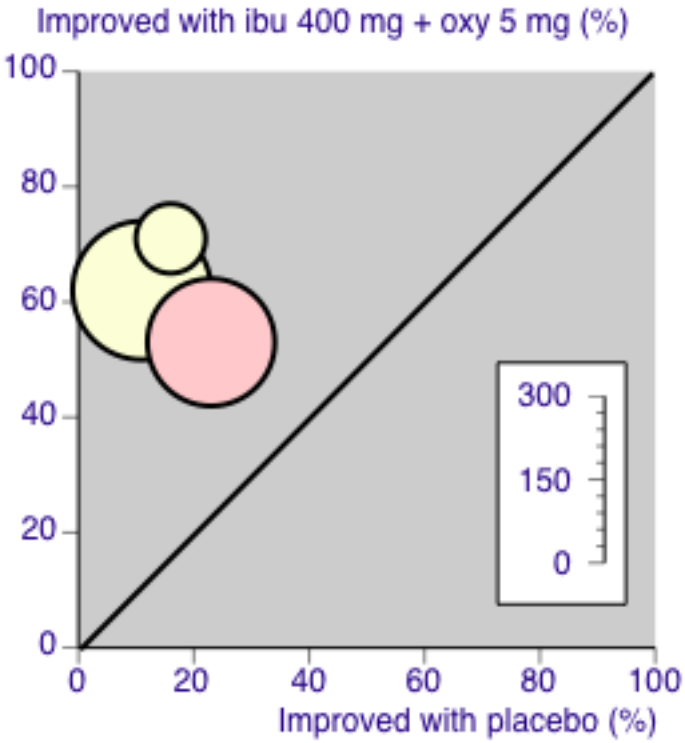
- The proportion of participants with ≥ 50% pain relief with ibuprofen + oxycodone was 58% (206/356, range 53% to 62%);
- The proportion of participants with ≥ 50% pain relief with oxycodone 5 mg was 23% (27/115, range 13% to 37%);
- The relative benefit of the combination compared with oxycodone alone was 2.5 (1.8 to 3.5); the NNT was 2.9 (2.3 to 4.0) (Analysis 3.1).

There were insufficient data for analysis of the combination versus paracetamol 325 mg + oxycodone 5 mg (123 participants), or versus paracetamol 500 mg + hydrocodone 7.5 mg (124 participants).

Subroup analysis

Only one dose of the combination was studied, so no analysis by dose was possible. There were insufficient data to allow any subgroup analysis by pain condition; one study (Singla 2005) enrolled participants following abdominal or pelvic surgery and the others following dental surgery (Figure 4).

Figure 4. L'Abbé plot showing ≥ 50% pain relief over 4 to 6 hours with ibuprofen 400 mg + oxycodone 5 mg and placebo in individual studies. Size of circle is proportional to size of study (inset scale). Pink circle = abdominal and pelvic surgery; cream circles = dental surgery.



Sensitivity analysis

All studies scored ≥ 3/5 on the Oxford Quality Score, so no sensitivity analysis for methodological quality was possible.
All comparisons involved treatment groups with between 50 and 199 participants, so no sensitivity analysis for small study size was possible.

Time to use of rescue medication

In the two studies in dental pain (Litkowski 2005; van Dyke 2004) the median time to use of rescue medication was greater than 6 hours for the ibuprofen + oxycodone combination, compared with 2.1 and 2.0 hours respectively for placebo. In the third study

(Singla 2005) in abdominal or pelvic surgery, the median time was 5.2 hours for the combination and 2.3 hours for placebo.

Participants using rescue medication

Ibuprofen 400 mg + oxycodone 5 mg versus placebo

All three studies reported the number of participants who used rescue medication over the study period (603 participants).

- The proportion of participants using rescue medication with ibuprofen + oxycodone was 40% (169/418, range 18% to 53%);
- The proportion of participants using rescue medication with placebo was 83% (153/185, range 73% to 92%);
- The relative benefit of the combination compared with placebo was 0.45 (0.39 to 0.52); the NNTp was 2.4 (2.0 to 2.9) (Analysis 1.2).

Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg alone

Two studies (Singla 2005; van Dyke 2004) reported the number of participants who used rescue medication over the study period (717 participants).

- The proportion of participants using rescue medication with ibuprofen + oxycodone was 44% (158/356, range 36% to 53%);
- The proportion of participants using rescue medication with ibuprofen alone was 53% (193/361, range 38% to 70%);
- The relative benefit of the combination compared with ibuprofen alone was 0.83 (0.72 to 0.97); the NNTp was 11 (6.1 to 56) (Analysis 2.2).

Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg alone

Two studies (Singla 2005; van Dyke 2004) reported the number of participants who used rescue medication over the study period (717 participants).

- The proportion of participants using rescue medication with ibuprofen + oxycodone was 44% (158/356, range 36% to 53%);
- The proportion of participants using rescue medication with oxycodone alone was 83% (95/115);
- The relative benefit of the combination compared with oxycodone alone was 0.53 (0.46 to 0.62); the NNTp was 2.6 (2.1 to 3.4) (Analysis 3.2).

Adverse events

Ibuprofen 400 mg + oxycodone 5 mg versus placebo

All studies reported the number of participants experiencing any adverse event with the combination compared with placebo (603 participants).

- The proportion of participants experiencing and adverse event with ibuprofen + oxycodone was 25% (105/418, range 11% to 41%);
- The proportion of participants experiencing and adverse event with placebo was 25% (47/185, range 11% to 55%);
- The relative risk of the treatment compared with placebo was 0.87 (0.66 to 1.2); the NNH was not calculated (Analysis 1.3).

The event rate in the study in abdominal or pelvic surgery (Singla 2005) was considerably higher in all active and placebo treatment arms than in the two dental surgery studies (Litkowski 2005; van Dyke 2004). Removing this study from the analysis gave a lower event rate in both treatment arms (14% with the combination, 11% with placebo), but did not significantly change the result (RR 1.2 (0.67 to 2.3).

Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg alone

Two studies (Singla 2005; van Dyke 2004) reported the number of participants experiencing any adverse event with the combination compared with ibuprofen alone (717 participants).

- The proportion of participants experiencing an adverse event with ibuprofen + oxycodone was 28% (98/356, range 16% to 41%);
- The proportion of participants experiencing an adverse event with ibuprofen alone was 26% (94/361, range 11% to 42%);
- The relative risk of the combination compared with ibuprofen alone was 1.1 (0.85 to 1.3); the NNH was not calculated (Analysis 2.3).

Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg alone

Two studies (Singla 2005; van Dyke 2004) reported the number of participants experiencing any adverse event with the combination compared with oxycodone alone (471 participants).

- The proportion of participants experiencing an adverse event with ibuprofen + oxycodone was 28% (98/356, range 16% to 41%);
- The proportion of participants experiencing an adverse event with oxycodone alone was 35% (40/115, range 27% to 44%);

- The relative risk of the combination compared with oxycodone alone was 0.78 (0.58 to 1.04); the NNH was not calculated (Analysis 3.3).

Serious adverse events

The two studies in dental pain (Litkowski 2005; van Dyke 2004) reported no serious adverse events. The study in abdominal or pelvic surgery reported a total of 11: 6/169 with the combination, 1/175 with ibuprofen alone, 3/52 with oxycodone alone, and 1/60 with placebo. None led to withdrawal, and none were considered related to study medication. They were likely to be a consequence of the more invasive and complicated surgery this group underwent.

Withdrawals

Withdrawals due to lack of efficacy are considered above, under Participants using rescue medication. All studies also reported on participants who withdrew for other reasons. These were uncommon (≤ 3%) and were due to treatment emergent adverse events, or in two cases a protocol violation and a withdrawal of consent.

DISCUSSION

The background to this review is a knowledge that combinations of different analgesics with different modes of action provide additive effects in acute pain and migraine (Moore 2011b; Moore 2012). The main thrust of this review is to assess the analgesic efficacy of ibuprofen and paracetamol combination analgesics because they are becoming available to the public without prescription, and combinations may be used to some extent in treating acute pain in hospital or in primary care.

Summary of main results

Three studies were identified for inclusion, all of which used only one dose combination. There were sufficient data to compare ibuprofen 400 mg + oxycodone 5 mg with placebo (603 participants), ibuprofen 400 mg alone (717 participants), and oxycodone alone (471 participants). There were insufficient data for analysis of comparisons with paracetamol + oxycodone and paracetamol + hydrocodone. The combination of ibuprofen and oxycodone at this dose provided better analgesia than placebo (60% versus 17% experiencing at least 50% pain relief over 6 hours; NNT 2.3 (2.0 to 2.8)), with a reduced need for additional analgesia over six hours (NNTp 2.4 (2.0 to 2.9)), and no increase in adverse events. When compared with the same dose of ibuprofen alone, the combination failed to reach a statistical superiority for pain relief (58% versus 50%; RR 1.2 (1.00 to 1.3)) but was better for use of rescue medication (NNTp 11 (6.1 to 56)). Compared with the same dose of oxycodone alone, the combination was significantly better for pain relief (58% versus 23%; NNT 2.5 (1.8 to 3.5) and use of rescue medication (NNTp 2.6 (2.1 to 3.4)).

In all comparisons adverse events were not significantly different between treatment groups, although single dose studies are not designed or adequately powered to reliably study adverse events. It was noticeable that the number of participants experiencing adverse events was higher in the study in abdominal and pelvic surgery than in the dental studies, and the only serious events were in this study. This almost certainly reflects the more complex and invasive nature of this type of surgery. Withdrawals for reasons other than lack of efficacy, and including those due to adverse events, were uncommon and did not differ between groups.

Overall completeness and applicability of evidence

The main limitation of the review is the relatively small number of studies and participants, and the use of only one dose combination. However, the general results are in accord with those known for ibuprofen and oxycodone alone (Derry 2009; Gaskell 2009) and for combination drugs in acute pain (Moore 2011b; Moore 2012).

Quality of the evidence

All studies were randomised and double-blind and provided information about withdrawals and dropouts, scoring at least 3/5 on the Oxford Quality Scale, indicating that they are likely to be methodologically robust. Studies were valid in that they recruited participants with adequate baseline pain, used clinically useful outcome measures, and had valid comparators. The studies themselves were of high quality, but sample sizes were somewhat limited.

Potential biases in the review process

We carried out extensive searches to identify relevant studies, but there always remains the possibility of unidentified studies. We calculated that for ibuprofen 400 mg plus oxycodone 5 mg, an additional 1494 participants would have to have been involved in unpublished trials with zero treatment effects for the NNT for at least 50% pain relief to increase above 8, a level we consider to be the limit of clinical utility for this outcome (Moore 2008). It is unlikely that this amount of unidentified information exists.

There are no other known potential biases in the review process.

Agreements and disagreements with other studies or reviews

We are unaware of any previous systematic reviews of ibuprofen plus oxycodone in acute pain in adults. The performance of ibuprofen and oxycodone alone in these studies is in close agreement with results in reviews of the individual drugs (Derry 2009; Gaskell 2009).

AUTHORS' CONCLUSIONS

Implications for practice

The combinations of ibuprofen 400 mg + oxycodone 5 mg is better than either drug alone. There were sufficient studies and participants, together with consistent large effects for pain, remedication, and adverse events, to consider that this is an important finding, as good analgesia was provided by relatively low doses of ibuprofen and oxycodone. In appropriate circumstances this combination might be useful.

Implications for research

It is not clear what are the implications for research. Studies offer no new methodological insights, and while additional data are always welcome, there are potential balancing ethical issues from including participants in studies that do not add to existing knowledge in a meaningful way. However, as these studies were largely confined to dental extraction in young participants, there is a need for additional studies in other postoperative situations, and especially in older, sicker patients.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Litkowski 2005

Methods	Multicentre, randomised, double-blind, 4 parallel groups, placebo and active controls. Single oral dose, Medication administered when baseline pain reached a moderate to severe intensity (≥ 50/100 mm) Pain assessed at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours
Participants	Surgical removal of ≥ 2 ipsilateral bony impacted third molars. N = 248. M = 108, F = 140. Mean age, 19 years.
Interventions	• Ibuprofen 400 mg + oxycodone 5 mg, n = 62. • Paracetamol 325 mg + oxycodone 5 mg, n = 61. • Paracetamol 500 mg + hydrocodone 7.5 mg, n = 62. • Placebo, n = 63.
Outcomes	PI- standard 4-point scale. PR- standard 5-point scale. PGE- standard 5-point scale. Use of rescue medication. Adverse events. Withdrawals.
Notes	Oxford Quality score: R1, DB1, W1. Total = 3/5. Rescue medication allowed after 2 hours.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described.
Size	Unclear risk	50 to 199 participants per treatment arm.

Singla 2005

Methods	Multicentre, randomised, double-blind, 4 parallel groups, placebo and active controls. Single oral dose Medication administered when baseline pain reached a moderate to severe intensity (≥ 50/100 mm) if within 6 hours of discontinuation of patient-controlled analgesia on morning following surgery Pain assessed at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours
Participants	Abdominal or pelvic surgery. N = 456. All F. Mean age, 42 years.
Interventions	• Ibuprofen 400 mg + oxycodone 5 mg, n = 169. • Ibuprofen 400 mg, n = 175. • Oxycodone 5 mg, n = 52. • Placebo, n = 60.
Outcomes	PI- standard 4-point scale. PR- standard 5-point scale. PGE- standard 5-point scale. Use of rescue medication. Adverse events. Withdrawals.
Notes	Oxford Quality score: R2, DB1, W1. Total = 4/5. Rescue medication allowed, timing not specified.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described.
Size	Unclear risk	50 to 199 participants per treatment arm.

van Dyke 2004

Methods	Multicentre, randomised, double-blind (double dummy), 4 parallel groups, placebo and active controls. Single oral dose Medication administered when baseline pain reached a moderate to severe intensity (≥ 50/100 mm) Pain assessed at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours
Participants	Surgical removal of ≥ 2 ipsilateral bony impacted third molars. N = 498. M = 219, F = 279. Mean age, 24 years.
Interventions	• Ibuprofen 400 mg + oxycodone 5 mg, n = 187. • Ibuprofen 400 mg, n = 186. • Oxycodone 5 mg, n = 63. • Placebo, n = 62.
Outcomes	PI- standard 4-point scale. PR- standard 5-point scale. PGE- standard 5-point scale. Use of rescue medication. Adverse events. Withdrawals.
Notes	Oxford Quality score: R1, DB2, W1. Total = 4/5. Rescue medication allowed after 2 hours.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-dummy".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-dummy".
Size	Unclear risk	50 to 199 participants per treatment arm.

DB - double blind, N - number of participants in study, n - number of participants in treatment arm, PGE - patient global evaluation, PI - pain intensity, PR - pain relief, R - randomised, W - withdrawals

DATA AND ANALYSES

Comparison 1. Ibuprofen 400 mg + oxycodone 5 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief at 6 hours	3	603	Risk Ratio (M-H, Fixed, 95% CI)	3.63 [2.60, 5.07]
2 Participants using rescue medication within 6 hours	3	603	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.39, 0.52]
3 Participants with any adverse event over 6 hours	3	603	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.15]

Comparison 2. Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief at 6 hours	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.00, 1.31]
2 Participants using rescue medication within 6 hours	2	717	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
3 Participants with any adverse event over 6 hours	2	717	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.85, 1.34]

Comparison 3. Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief at 6 hours	2	471	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [1.75, 3.46]
2 Participants using rescue medication within 6 hours	2	471	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.46, 0.62]
3 Participants with any adverse event over 6 hours	2	471	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.04]

Analysis 1.1. Comparison 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo, Outcome 1 Participants with ≥50% pain relief at 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo

Outcome: 1 Participants with ≥50% pain relief at 6 hours

Study or subgroup	Ibu/oxy n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Litkowski 2005	44/62	10/63		24.1 %	4.47 [2.48, 8.07]
Singla 2005	90/169	14/60		50.3 %	2.28 [1.41, 3.69]
van Dyke 2004	116/187	7/62		25.6 %	5.49 [2.71, 11.14]
Total (95% CI)	**418**	**185**		**100.0 %**	**3.63 [2.60, 5.07]**

Total events: 250 (Ibu/oxy), 31 (Placebo)

Heterogeneity: $Chi^2 = 5.39$, df = 2 (P = 0.07); $I^2 = 63\%$

Test for overall effect: Z = 7.59 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo, Outcome 2 Participants using rescue medication within 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo

Outcome: 2 Participants using rescue medication within 6 hours

Study or subgroup	Ibu/oxy n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Litkowski 2005	11/62	46/63		22.3 %	0.24 [0.14, 0.42]
Singla 2005	90/169	55/60		39.6 %	0.58 [0.49, 0.68]
van Dyke 2004	68/187	52/62		38.1 %	0.43 [0.35, 0.54]
Total (95% CI)	**418**	**185**		**100.0 %**	**0.45 [0.39, 0.52]**
Total events: 169 (Ibu/oxy), 153 (Placebo)					
Heterogeneity: Chi^2 = 14.60, df = 2 (P = 0.00067); I^2 =86%					
Test for overall effect: Z = 11.02 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo, Outcome 3 Participants with any adverse event over 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 1 Ibuprofen 400 mg + oxycodone 5 mg versus placebo

Outcome: 3 Participants with any adverse event over 6 hours

Study or subgroup	Ibu/oxy n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Litkowski 2005	7/62	7/63		10.5 %	1.02 [0.38, 2.73]
Singla 2005	69/169	33/60		73.6 %	0.74 [0.55, 0.99]
van Dyke 2004	29/187	7/62		15.9 %	1.37 [0.63, 2.98]
Total (95% CI)	**418**	**185**		**100.0 %**	**0.87 [0.66, 1.15]**

Total events: 105 (Ibu/oxy), 47 (Placebo)

Heterogeneity: Chi^2 = 2.58, df = 2 (P = 0.28); I^2 =22%

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg, Outcome 1 Participants with ≥50% pain relief at 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg

Outcome: 1 Participants with ≥50% pain relief at 6 hours

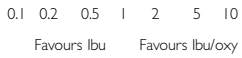
Study or subgroup	Ibu/oxy n/N	Ibu n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Singla 2005	90/169	77/175		41.8 %	1.21 [0.97, 1.51]
van Dyke 2004	116/187	105/186		58.2 %	1.10 [0.93, 1.30]
Total (95% CI)	**356**	**361**		**100.0 %**	**1.15 [1.00, 1.31]**

Total events: 206 (Ibu/oxy), 182 (Ibu)

Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 1.98 (P = 0.048)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg, Outcome 2 Participants using rescue medication within 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg

Outcome: 2 Participants using rescue medication within 6 hours

Study or subgroup	Ibu/oxy n/N	Ibu n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Singla 2005	90/169	123/175		63.3 %	0.76 [0.64, 0.90]
van Dyke 2004	68/187	70/186		36.7 %	0.97 [0.74, 1.26]
Total (95% CI)	**356**	**361**		**100.0 %**	**0.83 [0.72, 0.97]**

Total events: 158 (Ibu/oxy), 193 (Ibu)

Heterogeneity: Chi^2 = 2.40, df = 1 (P = 0.12); I^2 =58%

Test for overall effect: Z = 2.42 (P = 0.016)

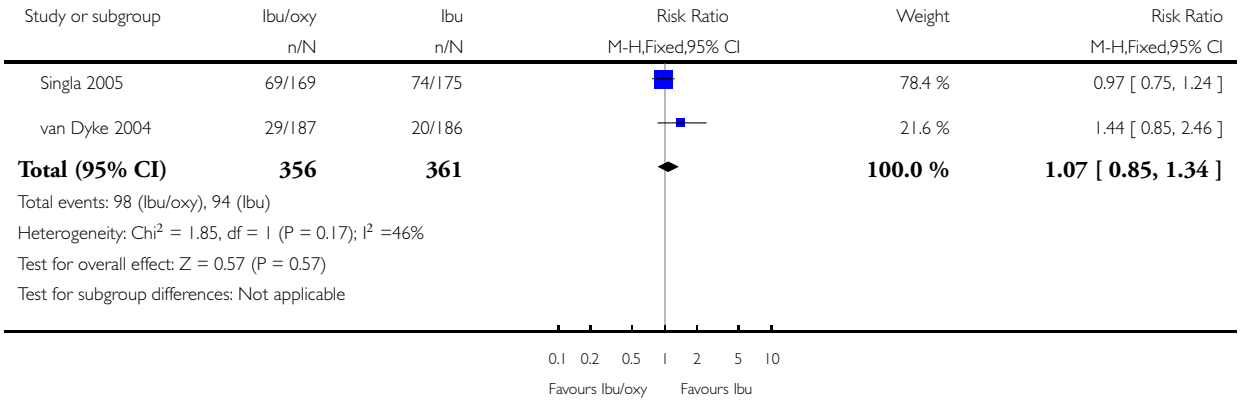
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg, Outcome 3 Participants with any adverse event over 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 2 Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400 mg

Outcome: 3 Participants with any adverse event over 6 hours



Analysis 3.1. Comparison 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg, Outcome 1 Participants with ≥50% pain relief at 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg

Outcome: 1 Participants with ≥50% pain relief at 6 hours

Study or subgroup	Ibu/oxy n/N	Oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Singla 2005	90/169	19/52		70.8 %	1.46 [0.99, 2.14]
van Dyke 2004	116/187	8/63		29.2 %	4.89 [2.53, 9.42]
Total (95% CI)	**356**	**115**		**100.0 %**	**2.46 [1.75, 3.46]**

Total events: 206 (Ibu/oxy), 27 (Oxy)

Heterogeneity: Chi^2 = 11.27, df = 1 (P = 0.00079); I^2 =91%

Test for overall effect: Z = 5.15 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg, Outcome 2 Participants using rescue medication within 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg

Outcome: 2 Participants using rescue medication within 6 hours

Study or subgroup	Ibu/oxy n/N	Oxy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Singla 2005	90/169	43/52		45.8 %	0.64 [0.53, 0.78]
van Dyke 2004	68/187	52/63		54.2 %	0.44 [0.35, 0.55]
Total (95% CI)	**356**	**115**		**100.0 %**	**0.53 [0.46, 0.62]**

Total events: 158 (Ibu/oxy), 95 (Oxy)

Heterogeneity: Chi^2 = 6.72, df = 1 (P = 0.01); I^2 =85%

Test for overall effect: Z = 8.53 (P < 0.00001)

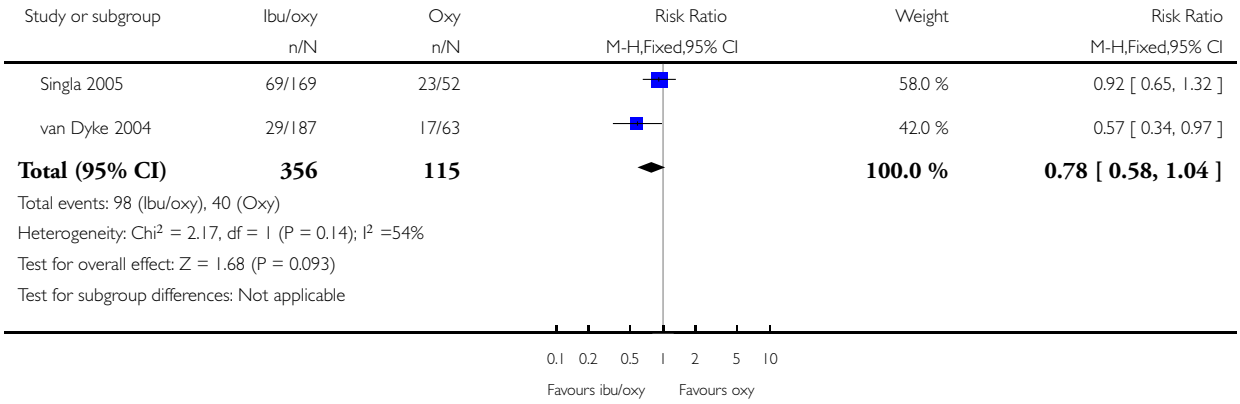
Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg, Outcome 3 Participants with any adverse event over 6 hours.

Review: Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults

Comparison: 3 Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg

Outcome: 3 Participants with any adverse event over 6 hours



APPENDICES

Appendix 1. CENTRAL search strategy

1. MeSH descriptor: [Ibuprofen] this term only
2. (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid)
3. MeSH descriptor: [Oxycodone] this term only
4. oxycodone
5. MeSH descriptor: [Pain, Postoperative] this term only
6. ((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or "post-operative analgesi*")
7. ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*))
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after")
9. (("post surg*" or post-surg*) and (pain* or discomfort))

10. ((pain* near/4 “after surg*”) or (pain* near/4 “after operat*”) or (pain* near/4 “follow* operat*”) or (pain* near/4 “follow* surg*”))
11. ((analgesi* near/4 “after surg*”) or (analgesi* near/4 “after operat*”) or (analgesi* near/4 “follow* operat*”) or (analgesi* near/4 “follow* surg*”))
12. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 1 or 2
15. 3 or 4
16. 14 and 15
17. 13 and 16

Appendix 2. MEDLINE (via OVID) search strategy

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Oxycodone/ or oxycodone.mp.
3. 1 and 2
4. Pain, Postoperative/
5. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or “post-operative analgesi*”).mp.
6. ((post-surgical adj4 pain*) or (“post surgical” adj4 pain*) or (post-surgery adj4 pain*)).mp.
7. (“pain-relief after surg*” or “pain following surg*” or “pain control after”).mp.
8. ((“post surg*” or post-surg*) and (pain* or discomfort)).mp.
9. ((pain* adj4 “after surg*”) or (pain* adj4 “after operat*”) or (pain* adj4 “follow* operat*”) or (pain* adj4 “follow* surg*”)).mp.
10. ((analgesi* adj4 “after surg*”) or (analgesi* adj4 “after operat*”) or (analgesi* adj4 “follow* operat*”) or (analgesi* adj4 “follow* surg*”)).mp.
11. exp Surgical Procedures, Operative/
12. or/2-9
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/11-18
22. 3 and 12 and 21

Appendix 3. EMBASE (viaOVID) search strategy

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Oxycodone/ or oxycodone.mp.
3. 1 and 2
4. Pain, Postoperative/
5. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or “post-operative analgesi*”).mp.
6. ((post-surgical adj4 pain*) or (“post surgical” adj4 pain*) or (post-surgery adj4 pain*)).mp.
7. (“pain-relief after surg*” or “pain following surg*” or “pain control after”).mp.
8. ((“post surg*” or post-surg*) and (pain* or discomfort)).mp.
9. ((pain* adj4 “after surg*”) or (pain* adj4 “after operat*”) or (pain* adj4 “follow* operat*”) or (pain* adj4 “follow* surg*”)).mp.
10. ((analgesi* adj4 “after surg*”) or (analgesi* adj4 “after operat*”) or (analgesi* adj4 “follow* operat*”) or (analgesi* adj4 “follow* surg*”)).mp.

11. exp Surgical Procedures, Operative/
12. or/4-11
13. random*.tw.
14. factorial*.tw.
15. crossover*.tw.
16. cross over*.tw.
17. cross-over*.tw.
18. placebo*.tw.
19. (doubl* adj blind*).tw.
20. assign*.tw.
21. allocat*.tw.
22. Crossover Procedure/
23. double-blind procedure.tw.
24. Randomized Controlled Trial/
25. or/13-24
26. 3 and 12 and 25

Appendix 4. Glossary

Categorical rating scale: The commonest is the five category scale (none, slight, moderate, good or lots, and complete). For analysis, numbers are given to the verbal categories (for pain intensity, none = 0, mild = 1, moderate = 2 and severe = 3; and for relief, none = 0, slight = 1, moderate = 2, good or lots = 3 and complete = 4). Data from different subjects are then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means). The validity of converting categories into numerical scores was checked by comparison with concurrent visual analogue scale measurements. Good correlation was found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

VAS: Visual analogue scale: For pain intensity, lines with left end labelled "no pain" and right end labelled "worst pain imaginable", and for pain relief, lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain" seem to overcome the limitation of forcing patient descriptors into particular categories. Patients mark the line at the point that corresponds to their pain or pain relief. Scores are obtained by measuring the distance between the no relief end and the patient's mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. Greater concentration and coordination are needed, which can be difficult postoperatively or with neurological disorders.

TOTPAR: Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic and maintained that level of pain relief for six hours, he or she would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

SPID: Summed pain intensity difference (SPID) is calculated as the sum of the differences between pain scores and baseline pain score over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the trapezoidal rule.

VAS TOTPAR and **VAS SPID** are visual analogue versions of TOTPAR and SPID.

See "Measuring pain" in Bandolier's Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13 (Moore 2003).

Appendix 5. Summary of outcomes: analgesia and use of rescue medication

		Analgesia		Rescue medication	
Study ID	**Treatment**	**PR**	**Number with 50% PR**	**Median time to use (h)**	**Number using**
Litkowski 2005	(1) Ibu 400 mg + oxy 5 mg, n = 62 (2) Paracet 325 mg + oxy 5 mg, n = 61 (3) Paracet 500 mg + hydrocodone 7.5 mg, n = 62 (4) Placebo, n = 63	TOTPAR 6: (1) 14.98 (2) 9.53 (3) 8.36 (4) 5.05	(1) 44/62 (2) 25/61 (3) 22/62 (4) 10/63	(1) > 6 (2) > 6 (3) 4.17 (4) 2.14	(1) 11/62 (2) 30/61 (3) 38/62 (4) 46/63
Singla 2005	(1) Ibu 400 mg + oxy 5 mg, n = 169 (2) Ibu 400 mg, n = 175 (3) Oxy 5 mg, n = 52 (4) Placebo, n = 60	TOTPAR 6: (1) 11.75 (n = 168) (2) 10.03 (n = 174 (3) 8.56 (4) 6.41	(1) 90/169 (2) 77/175 (3) 19/52 (4) 14/60	(1) 5.23 (2) 3.95 (3) 2.50 (4) 2.28	(1) 90/169 (2) 123/175 (3) 43/52 (4) 55/60
van Dyke 2004	(1) Ibu 400 mg + oxy 5 mg, n = 187 (2) Ibu 400 mg, n = 186 (3) Oxy 5 mg, n = 63 (4) Placebo, n = 62	TOTPAR 6: (1) 13.3 (2) 12.2 (3) 4.3 (4) 4.2	(1) 116/187 (2) 105/186 (3) 8/63 (4) 7/62	(1) > 6 (2) > 6 (3) 2.1 (4) 2.03	(1) 68/187 (2) 70/186 (3) 52/63 (4) 52/62

Ibu = ibuprofen; Oxy = oxycodone; PR = pain relief; TOTPAR = total pain relief

Appendix 6. Summary of outcomes: adverse events and withdrawals

		Adverse events		
Study ID	**Treatment**	**Any**	**Serious**	**Withdrawals**
Litkowski 2005	(1) Ibu 400 mg + oxy 5 mg, n = 62 (2) Paracet 325 mg + oxy 5 mg, n = 61 (3) Paracet 500 mg + hydrocodone 7.5 mg, n = 62 (4) Placebo, n = 63	(1) 7/62 (2) 17/61 (3) 16/63	None	(1) 0/62 (2) 0/61 (3) 2/63 (AE and withdrew consent) (4) 1/63 (AE)

(*Continued*)

Singla 2005	(1) Ibu 400 mg + oxy 5 mg, n = 169 (2) Ibu 400 mg, n = 175 (3) Oxy 5 mg, n = 52 (4) Placebo, n = 60	(1) 69/169 (2) 74/175 (3) 23/52 (4) 33/60	(1) 6/169 (2) 1/175 (3) 3/52 (4) 1/60 None led to withdrawal, none related to study medication	(1) 4/169 (AE) (2) 2/175 (AE, protocol violation) (3) 1/52 (AE) (4) 0/60
van Dyke 2004	(1) Ibu 400 mg + oxy 5 mg, n = 187 (2) Ibu 400 mg, n = 186 (3) Oxy 5 mg, n = 63 (4) Placebo, n = 62	(1) 29/187 (2) 20/186 (3) 17/63 (4) 7/62	None	2 participants in (1) withdrew due to AEs (nausea + vomiting and nausea)

AE = adverse event; Ibu = ibuprofen; Oxy = oxycodone.

WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
2 October 2017	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 12, 2012

Review first published: Issue 6, 2013

Date	Event	Description
17 June 2015	Review declared as stable	This review will be assessed for further updating in 2017.

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing the protocol. CD and SD carried out searches, assessed studies for inclusion, and extracted data. RAM acted as arbitrator, and SD entered data into RevMan. All authors were involved in analysis and writing the review. RAM will be responsible for updating the review.

DECLARATIONS OF INTEREST

RAM and SD have received research support from charities, government and industry sources at various times. RAM has consulted for various pharmaceutical companies and has received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. CD has no interests to declare.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The published protocol specified a lower age limit for participants of 15 years. One study (Litkowski 2005) included participants aged 12 years or more, but the mean age was 19 years with the lower limit of the standard deviation of 15 years, suggesting that very few individuals were younger than 15 years. We decided to include the study so as not to discard a large amount of information that was unlikely to be unduly influenced by inclusion of a very small number of under-age participants.

NOTES

A restricted search in September 2017 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage; adverse effects]; Analgesics, Opioid [*administration & dosage; adverse effects]; Drug Combinations; Ibuprofen [*administration & dosage; adverse effects]; Oxycodone [*administration & dosage; adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans